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Clinical implications of oncological resectability criteria in hepatocellular carcinoma treated with transarterial chemoembolization

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Abstract

Background

The oncological resectability criteria for hepatocellular carcinoma (BR-HCC) have mainly been evaluated in surgical populations, and their clinical relevance in patients undergoing transarterial chemoembolization (TACE) remains unclear. This study evaluated the prognostic significance and clinical implications of the BR-HCC criteria in TACE-treated patients.

Methods

We retrospectively analyzed the data of 1,018 patients with HCC who underwent initial treatment between 2014 and 2023, including 222 patients treated with TACE and 638 patients who underwent liver resection (LR) as a reference cohort. Patients were classified into resectable (R), borderline resectable 1 (BR1), and borderline resectable 2 (BR2) groups according to pre-treatment imaging findings. Overall survival (OS) and time to treatment failure (TTF) were analyzed using Kaplan–Meier and Cox regression analyses.

Results

The BR-HCC criteria successfully stratified prognosis in the TACE cohort. The median OS was 50.0, 28.2, and 10.0 months in the R, BR1, and BR2 groups, respectively ($P < 0.05$), with similar trends observed for TTF. Impaired liver function, elevated AFP levels, and macrovascular invasion were independently associated with poor OS. Hepatic adverse events after TACE occurred significantly more frequently in the BR1/BR2 groups than in the R group. Exploratory propensity score–matched analyses demonstrated longer OS after LR than after TACE within the BR cohort.

Conclusions

The BR-HCC criteria provide clinically meaningful prognostic stratification in patients undergoing TACE and may help identify patients less suitable for repeated TACE-based strategies, thereby supporting individualized multidisciplinary treatment approaches, including systemic therapy.

Introduction

Hepatocellular carcinoma (HCC) treatment has evolved substantially in recent years owing to advances in systemic therapies and the increasing adoption of multidisciplinary treatment strategies [1–5]. As therapeutic options have expanded, the optimal selection and sequencing of locoregional and systemic treatments have become increasingly important in clinical practice [6].

In Japan, radiofrequency ablation (RFA), liver resection (LR), and transarterial chemoembolization (TACE) have traditionally been the principal treatment modalities for HCC [7]. Historically, TACE has served as an effective locoregional therapy for patients deemed unsuitable for LR because of impaired liver function or unfavorable oncological factors [7, 8]. However, recent advances in systemic therapies have redefined the roles of LR and TACE [1, 9]. In the modern treatment era, TACE is increasingly combined with systemic therapies to improve intrahepatic disease control and clinical outcomes [3, 4, 10]. Nevertheless, patient selection for TACE remains heterogeneous, and reliable tools for pre-treatment risk stratification are lacking.

To address this issue, novel oncological resectability criteria for HCC (BR-HCC criteria) were established through a Japanese expert consensus in 2023 [11]. Because the traditional concept of unresectability remains insufficiently defined, borderline resectability was subdivided into two categories according to therapeutic considerations related to LR. Accordingly, HCC was classified into three categories: resectable (R), borderline resectable 1 (BR1), and borderline resectable 2 (BR2). Although previous studies have evaluated LR and systemic therapy using this framework [9, 12], its broader applicability across different treatment modalities remains unclear, particularly in patients undergoing TACE.

Because the BR-HCC criteria are based on tumor-related imaging findings, they may provide a practical tool for prognostic stratification in patients treated with TACE and facilitate individualized multidisciplinary treatment planning. Therefore, this study aimed to evaluate the prognostic significance of the BR-HCC criteria in patients undergoing TACE. In addition, we explored the association between oncological classification and clinically relevant factors, including liver function, tumor markers, and treatment-related hepatic adverse events (AEs). Outcomes in patients undergoing LR were analyzed as a reference cohort for contextual interpretation.

Patients and Methods

Study design and population

This retrospective study included 1018 patients who underwent initial treatment for primary HCC at Nihon University Itabashi Hospital, Japan, between January 2014 and December 2023. Patients treated with RFA (n = 128) or systemic therapy alone (n = 30) were excluded to focus on locoregional treatment strategies. The final cohort included 222 patients treated with TACE and 638 who underwent LR, the latter serving as a reference cohort (Fig. 1).

Definition of BR-HCC criteria and macrovascular invasion

Patients were classified into resectable (R), borderline resectable 1 (BR1), and borderline resectable 2 (BR2) groups according to the BR-HCC criteria based on pre-treatment imaging [11]. Macrovascular invasion was defined according to the Japanese staging system (Vp2–4, Vv2–3, or B2–4).

Patient characteristics

HCC was diagnosed using dynamic computed tomography (CT), gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced magnetic resonance imaging (MRI), and/or contrast-enhanced ultrasonography with perflubutane. Tumor number, maximum diameter, and vascular invasion were evaluated radiologically before treatment. Clinical variables included age, sex, etiology of liver disease, hematological parameters, and serum levels of total bilirubin, albumin, ammonia, alpha-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP), and prothrombin time/international normalized ratio. Liver function was assessed using the Child–Pugh classification and modified albumin-bilirubin (mALBI) grade [13].

The study protocol was approved by the Institutional Review Board of Nihon University (RK-211012-5) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained using the opt-out method because of the retrospective study design.

Treatment strategy

Treatment strategies were determined according to the Clinical Practice Guidelines for Hepatocellular Carcinoma issued by the Japan Society of Hepatology [7] and institutional multidisciplinary discussions involving hepatologists and surgeons. Treatment selection was based on tumor burden, liver function, and technical feasibility. In general, TACE was selected for patients deemed unsuitable for curative-intent treatments, including LR and RFA, because of oncological or clinical factors. Between 2014 and 2017, TACE was mainly selected when neither LR nor RFA was indicated. Following approval of lenvatinib in 2018, systemic therapies, including tyrosine kinase inhibitors and immune checkpoint inhibitors, were incorporated into treatment strategies in combination with TACE when appropriate.

Indication and procedure for TACE therapy

Indications for TACE included: (1) unresectable HCC unsuitable for other locoregional therapies; (2) Eastern Cooperative Oncology Group performance status ≤ 2; (3) Child–Pugh class A or B; and (4) preserved hematological and renal function [14]. A catheter was selectively advanced into the hepatic artery supplying the tumor, followed by injection of an emulsion of cisplatin or epirubicin mixed with Lipiodol. Maximum doses were 65 mg/m² for cisplatin, 60 mg/m² for epirubicin, and 0.3 mL/kg for Lipiodol [8].

Follow-up and outcome measures

Tumor assessment was performed using contrast-enhanced CT or MRI within 14 days before treatment initiation and every 3 months thereafter following an initial evaluation at 1 month. Lesions ≥ 10 mm were considered measurable; up to five target lesions were selected per patient.

Repeat TACE using the same chemotherapeutic agent was performed for intrahepatic progression, including recurrence of treated lesions or newly developed lesions. Tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC [15]. The objective response rate (ORR) was defined as the proportion of patients achieving complete response (CR) or partial response (PR), whereas the disease control rate included CR, PR, and stable disease (SD).

Recurrence after LR was diagnosed radiologically using dynamic CT and/or MRI [16], and recurrent HCC was treated according to tumor status and liver function. Overall survival (OS) was defined as the interval between initial treatment and death from any cause. Time-to-treatment failure (TTF) was defined as the interval from initiation of TACE to untreatable progression or death.

TACE-related AEs were retrospectively assessed throughout the entire TACE treatment course and follow-up period and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Serious AEs were defined as grade ≥ 3. TACE-related mortality was defined as death due to treatment-related complications within 4 weeks after TACE.

Statistical analysis

All analyses were based on the initial treatment modality irrespective of subsequent therapies. Statistical analyses were performed using JMP software (v14.0.1; SAS Institute, Cary, NC, USA), with $P < 0.05$ considered statistically significant. Continuous variables were compared using the Mann–Whitney *U* test and categorical variables using the χ^2 test or Fisher's exact test, as appropriate. Survival outcomes were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models were used for multivariable analyses.

As an exploratory analysis, propensity score (PS) matching was performed to compare outcomes between LR and TACE in the BR cohort. Twelve variables were included in the model: age, sex, etiology, platelet count, AFP, DCP, ALBI score, tumor diameter, tumor number, macrovascular invasion, BR category, and treatment era (2014–2017 vs. 2018–2023) [12, 17]. One-to-one matching was performed using a caliper width of 0.2. Given the retrospective design and differences in treatment indication, these analyses were considered hypothesis-generating [18].

Results

Prognostic stratification by BR-HCC criteria, with a focus on the TACE cohort

Among the patients treated with TACE, 100 (45.0%), 51 (23.0%), and 71 (32.0%) were classified into the R, BR1, and BR2 groups, respectively. The median OS was 50.0 months in the R group, 28.2 months in the BR1 group, and 10.0 months in the BR2 group, demonstrating a stepwise decline across categories ($P < 0.05$; Fig. 2A). Similarly, the median TTF decreased from 41.0 months in the R group to 18.7 months in the BR1 group and 4.2 months in the BR2 group ($P < 0.05$; Fig. 2B).

Similar prognostic trends were observed in the LR cohort. In the LR group, 528 (82.8%), 59 (9.2%), and 51 (8.0%) patients were categorized as R, BR1, and BR2, respectively ($P < 0.05$; Supplementary Fig. 1).

Clinicopathological characteristics and prognostic factors in the BR cohort

Within the BR cohort, patients treated with TACE had more advanced tumor characteristics than those of patients undergoing LR, including higher tumor number ($P = 0.002$) and more frequent macrovascular invasion ($P < 0.001$) (Table 1). Liver function was also poorer in the TACE group, as reflected by higher ALBI scores.

In multivariable analysis of the TACE cohort, impaired liver function (mALBI grade 2b/3; HR 2.04, $P = 0.004$), elevated AFP levels (HR 1.32 per log increase, $P < 0.001$), and macrovascular invasion (HR 1.68, $P = 0.040$) were independently associated with poor OS (Table 2). Impaired liver function (HR 1.87, $P = 0.005$) and extrahepatic metastasis (HR 3.61, $P < 0.001$) were independently associated with shorter TTF. Prognostic factors identified in the LR cohort are summarized in Supplementary Table 1.

The baseline characteristics of the patients with BR1 and BR2 disease treated with TACE are summarized in Table 3. Combination therapy with lenvatinib was administered in 11.8% (6/51) of BR1 patients and 8.5% (6/71) of BR2 patients; the difference was not significant ($P = 0.555$).

Exploratory comparison within the BR cohort

The demographic characteristics of all the patients undergoing TACE and LR are shown in Supplementary Table 2. As an exploratory analysis, outcomes between LR and TACE were compared in the BR cohort using PS matching (Table 1). After matching, 59 patient pairs with balanced covariates were generated (Supplementary Table 3).

Before matching, the median OS was 18.4 months in the TACE group and 47.3 months in the LR group ($P < 0.001$; Supplementary Fig. 2A). After PS matching, the median OS was 24.7 months in the TACE group and was not reached in the LR group (Supplementary Fig. 2B). The LR group demonstrated significantly better OS than that of the TACE group (HR 2.41; 95% CI, 1.42–4.23; $P = 0.001$).

Tumor responses

In the R group, 24 patients achieved CR and 15 achieved PR, yielding an ORR of 39.0% (39/100) according to the mRECIST. In contrast, ORR was 9.8% (5/51) in the BR1 group and 1.4% (1/71) in the BR2 group (Table 4). Post-progression treatments after TACE according to BR-HCC classification are shown in Fig. 3. More than 70% of patients in each subgroup subsequently received systemic therapy during follow-up.

Adverse events for the TACE cohort

The treatment-related AEs during the entire TACE treatment course are summarized in Table 5. Four patients died within 30 days after TACE; however, all deaths were attributed to cancer progression, and

no treatment-related mortality was observed. Grade ≥3 increased ALP levels and hypoalbuminemia were more frequently observed in BR1/BR2 patients than in R patients (P = 0.011 and P = 0.015, respectively). No significant differences were observed for other AEs. Major hepatic AEs, including massive ascites and hepatic encephalopathy, were significantly more frequent in BR2 patients [17/71 (23.9%)] than in R patients [7/100 (7.0%)] (P = 0.002), whereas no significant difference was observed between the R and BR1 groups [8/51 (15.7%)] (P = 0.101).

Discussion

Previous studies have evaluated the prognostic utility of the BR-HCC criteria, proposed by a Japanese expert consensus in 2023, mainly in surgical populations [11, 17]. In the present study, the BR-HCC classification clearly stratified both OS and TTF in patients treated with TACE, supporting its applicability beyond surgical settings. To our knowledge, this is the first study to demonstrate the prognostic relevance of the BR-HCC criteria in a TACE cohort. The stepwise deterioration in outcomes from R to BR1 and BR2 suggests that this classification reflects tumor aggressiveness and therapeutic resistance even among patients undergoing non-curative locoregional treatment.

The present findings also suggest that the BR-HCC classification may have practical implications for treatment selection in patients undergoing TACE. In particular, patients classified as BR2 showed markedly poor survival and rapid treatment failure, indicating that TACE alone may be insufficient for disease control in this subgroup. In the era of evolving systemic therapies, including immune checkpoint inhibitor–based regimens [5, 10], these patients may be better candidates for upfront systemic treatment or multidisciplinary strategies rather than repeated TACE. In contrast, patients in the BR1 category may represent a more heterogeneous population in whom TACE-based approaches, potentially combined with systemic therapy, could provide disease control and serve as a bridge to conversion therapies, including surgical resection [19, 20]. Meanwhile, patients classified as R showed relatively favorable outcomes, suggesting that TACE remains a reasonable option in selected cases where curative treatments are not feasible [21]. Taken together, the BR-HCC classification may serve not only as a prognostic tool but also as a framework for individualized multidisciplinary treatment strategies in HCC.

In addition to poor oncological outcomes, patients classified as BR1/BR2 experienced a significantly higher incidence of hepatic AEs following TACE. This finding is clinically important because preservation of hepatic functional reserve is a key determinant of eligibility for subsequent treatments in HCC. The combination of shorter TTF, inferior OS, and increased hepatic toxicity suggests that repeated TACE may provide limited benefit in these patients, particularly in the BR2 subgroup. Furthermore, the markedly lower ORR observed in BR2 supports the limited efficacy of repeated TACE in this population. These findings support the concept that the BR-HCC classification may help identify patients who are less suitable for TACE-based strategies and who may benefit from earlier introduction of systemic or multidisciplinary treatment approaches [22].

Hepatocellular carcinoma is a heterogeneous disease in which treatment decisions are influenced by tumor burden, vascular invasion, and liver function [23]. Although multiple staging systems exist [1, 6], no standardized framework is established for defining oncological resectability. The BR-HCC criteria were developed to address this gap through a tumor-based classification. While prior studies mainly focused on surgical populations [9], our findings extend the utility of this framework to patients undergoing TACE, suggesting its value for oncological stratification in contemporary practice. In the present study, impaired liver function (mALBI grade 2b/3), elevated AFP levels, and macrovascular invasion were independently associated with poor OS in the TACE cohort, highlighting the combined influence of tumor burden, tumor biology, and hepatic reserve on prognosis [24, 25]. Macrovascular invasion was particularly associated with unfavorable outcomes in the BR2 subgroup. Together with the increased incidence of hepatic AEs in the BR population, these findings suggest that careful patient selection is required when considering repeated TACE in advanced HCC [26].

Recent advances in systemic therapies, particularly immune checkpoint inhibitor–based regimens, have substantially changed the treatment landscape of advanced HCC [5, 10]. In this setting, preservation of liver function has become increasingly important to maintain eligibility for subsequent systemic or conversion therapies. Accordingly, TACE is increasingly incorporated into combination or sequential strategies rather than being used as standalone treatment [27]. Consistent with this contemporary treatment paradigm, more than 70% of patients in each BR-HCC subgroup subsequently received systemic therapy during follow-up. Our findings suggest that the BR-HCC classification may provide useful information not only regarding prognosis but also regarding the risk of treatment-related hepatic deterioration after TACE. Therefore, this classification may contribute to treatment sequencing decisions in multidisciplinary HCC management, including the identification of patients who may benefit more from systemic therapy than from repeated locoregional treatment.

In exploratory analyses, differences in survival outcomes between treatment modalities were observed within the BR cohort. However, this comparison was not intended to determine treatment superiority because treatment allocation was strongly influenced by clinical judgment, liver function, tumor burden, and technical feasibility. Rather, the analysis was performed to provide a contextual interpretation of the BR-HCC framework across treatment modalities for HCC. Given the retrospective design and potential residual confounding, these findings should be interpreted cautiously. Nevertheless, the results highlight the importance of appropriate patient stratification and treatment sequencing in contemporary HCC management.

This study has certain limitations. First, this was a retrospective single-center study, and selection bias in treatment allocation was unavoidable. In particular, patients undergoing TACE tended to have more advanced disease and poorer liver function, which may limit the generalizability of the findings. Although PS matching was performed, residual confounding could not be fully eliminated. Second, treatment indications were based on institutional criteria and may not have been fully standardized, further limiting external validity. Third, treatment strategies evolved during the study period, particularly following the introduction of novel systemic therapies, which may have influenced clinical outcomes. In addition,

because patients treated with upfront systemic therapy alone were excluded, the optimal selection between TACE and systemic therapy could not be directly determined. Finally, TACE represents a therapeutic approach distinct from curative-intent treatments such as LR or RFA and occupies an intermediate position within the treatment algorithm; therefore, direct comparisons between treatment modalities should be interpreted cautiously [1, 27].

In conclusion, the BR-HCC criteria provide clinically meaningful prognostic stratification in patients undergoing TACE. This classification may serve as a useful tool for risk assessment and treatment planning in heterogeneous HCC populations. Furthermore, the increased incidence of hepatic AEs observed in BR1/BR2 patients suggests that the BR-HCC framework may help identify populations less suitable for repeated TACE-based strategies. Further prospective multicenter studies are warranted to validate these findings and clarify the role of the BR-HCC framework in guiding multidisciplinary treatment strategies in the modern systemic therapy era.

Declarations

Conflict of interest

The authors declare no conflicts of interest.

Ethics approval

The study protocol was approved by the Institutional Review Board of Nihon University (Approval No. RK-211012-5) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent for participation was obtained using an opt-out method.

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The authors have nothing to report.

Author contributions

Hayato Abe: Conceptualization; data curation; formal analysis; methodology; writing – original draft. Yukiyasu Okamura: Conceptualization; project administration; formal analysis; resources; supervision; writing – review and editing. Osamu Aramaki: Writing – review and editing. Nao Yoshida: Data curation; writing – review and editing. Yusuke Mitsuka: Data curation; investigation; software; validation. Shu Inagaki: Conceptualization; data curation; investigation. Masataka Shindate: Supervision; writing – review and editing. Shunsuke Yamagishi: Data curation; visualization. Yasuhiro Okumura: Writing – review and editing. Kosuke Narumiya: Writing – review and editing. Masamichi Moriguchi: Conceptualization; data curation; formal analysis; supervision; writing – review and editing. All the authors have approved the final version of this article.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

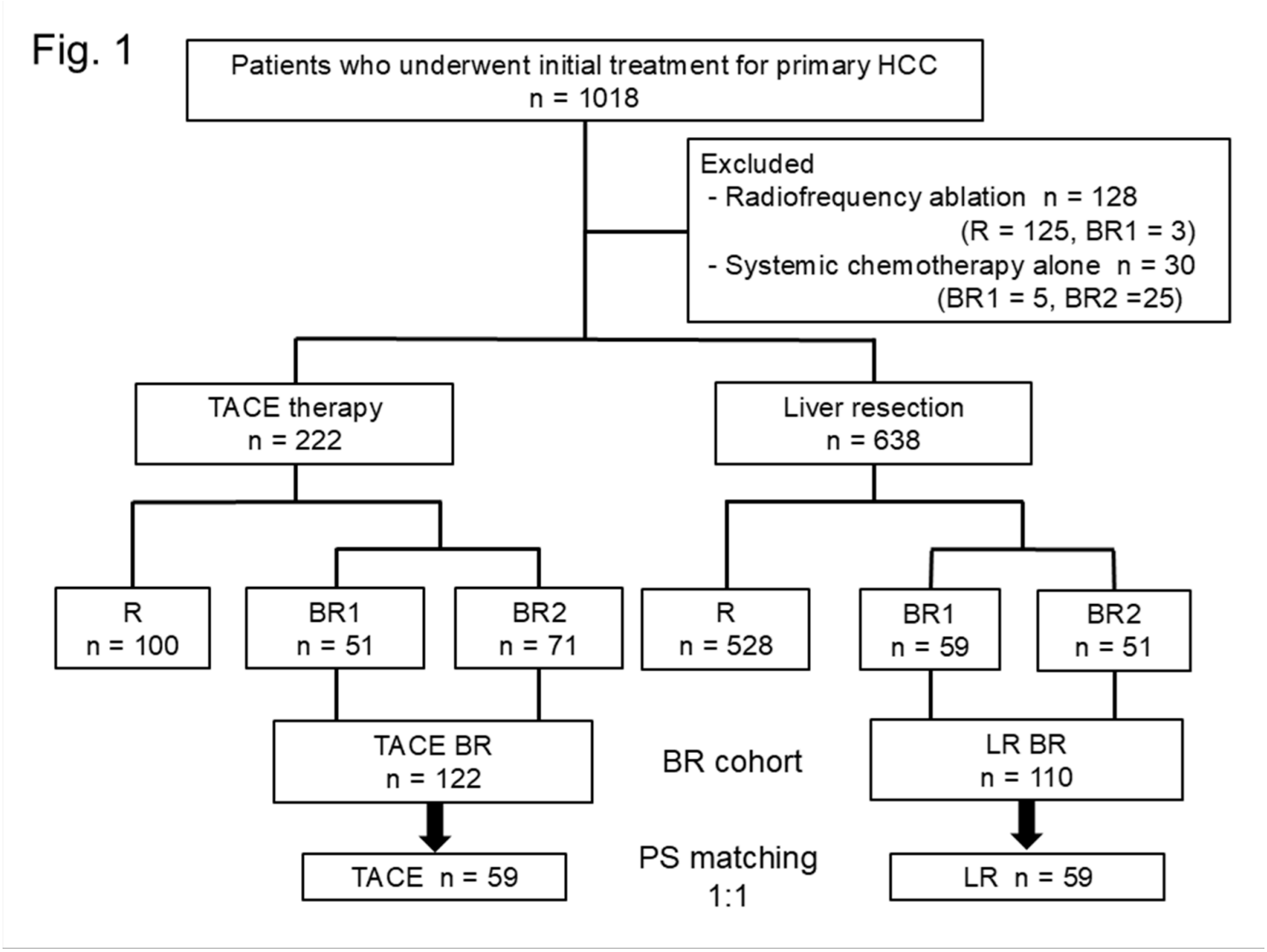

Figure 1

Flowchart of the study population.

Patients were classified into resectable (R), borderline resectable 1 (BR1), and borderline resectable 2 (BR2) groups based on the BR-HCC criteria.

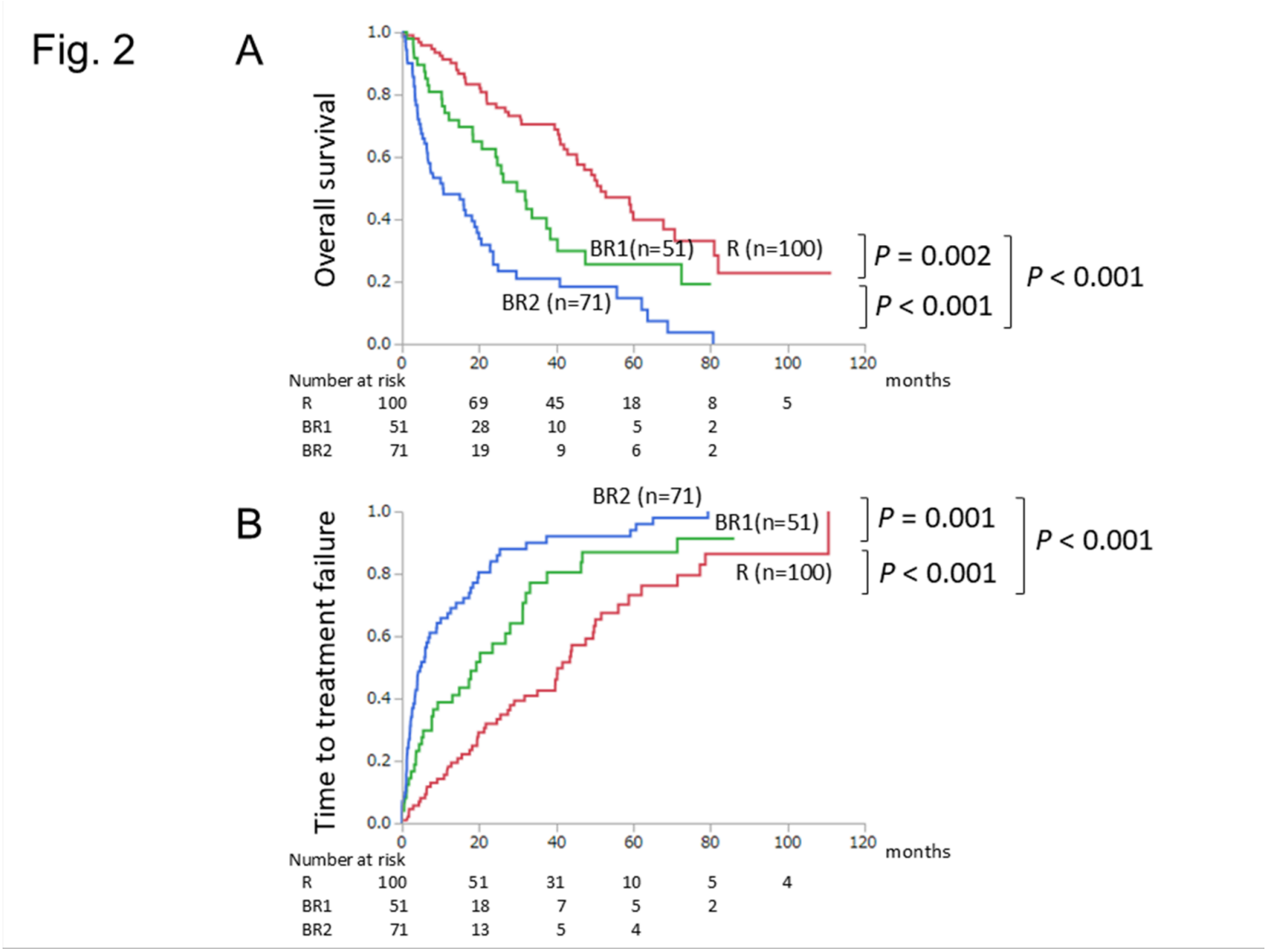

Figure 2

Kaplan–Meier curves of (A) overall survival (OS) and (B) time to treatment failure (TTF) in patients undergoing transarterial chemoembolization (TACE), stratified by BR-HCC classification. Survival outcomes show a stepwise decline from R to BR1 and BR2 groups. BR, borderline resectable; HCC, hepatocellular carcinoma.

Fig. 3

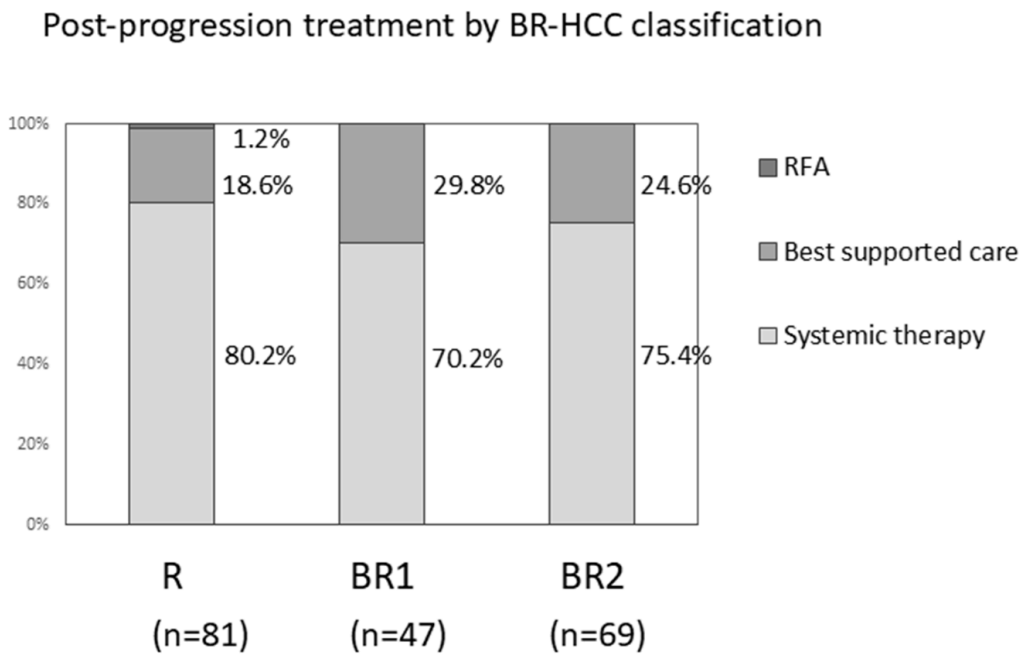

Figure 3

Post-progression treatment by BR-HCC classification. BR, borderline resectable; HCC, hepatocellular carcinoma; RFA. radiofrequency ablation.

Supplementary Files

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